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## Effect of Disodium Cromoglycate (DSCG) and Antihistamines on Postirradiation Cerebral Blood Flow and Plasma Levels of Histamine and Neurotensin<sup>1</sup>

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Effect of Disodium Cromoglycate (DSCG) and Antihistamines on Postirradiation Cerebral Blood Flow and Plasma Levels of Histamine and Neurotensin. COCKERHAM, L. G., PAUTLER, E. L., CARRAWAY, R. E., COCHRANE, D. E., AND HAMPTON, J. D. (1988). *Fundam. Appl. Toxicol.* 10, 233-242. In an attempt to elucidate mechanisms underlying the irradiation-induced decrease in regional cerebral blood flow (rCBF) in primates, hippocampal and visual cortical blood flows of rhesus monkeys were measured by hydrogen clearance, before and after exposure to 100 Gy, whole-body,  $\gamma$  irradiation. Systemic blood pressures were monitored simultaneously. Systemic arterial plasma histamine and neurotensin levels were determined preirradiation and postirradiation. Compared to control animals, the irradiated monkeys exhibited an abrupt decline in systemic blood pressure to 23% of the preirradiation level within 10 min postirradiation, falling to 12% by 60 min. A decrease in hippocampal blood flow to 32% of the preirradiation level was noted at 10 min postirradiation, followed by a slight recovery to 43% at 30 min and a decline to 23% by 60 min. The cortical blood flow for the same animals showed a steady decrease to 29% of the preirradiation levels by 60 min postirradiation. Animals given the mast cell stabilizer disodium cromoglycate and the antihistamines mepyramine and cimetidine before irradiation did not exhibit an abrupt decline in blood pressure but displayed a gradual decrease to a level 33% below preirradiation levels by 60 min postirradiation. Also, the treated, irradiated monkeys displayed rCBF values that were not significantly different from the nonirradiated controls. The plasma neurotensin levels in the irradiated animals, treated and untreated, indicated a nonsignificant postirradiation increase above control levels. However, the postirradiation plasma histamine levels in both irradiated groups showed an increase of approximately 1600% above the preirradiation levels and the postirradiation control levels. These findings implicate histamine in the postirradiation hypotension, but not necessarily in the direct responsibility for the decrease in regional cerebral blood flow seen immediately postirradiation in the primate. © 1988 Society of Toxicology.

Some of the many consequences which result from exposure to high levels of ionizing radiation are dramatic changes in the ability of an animal to perform a trained task. Early tran-

sient incapacitation (ETI), characterized as a complete but temporary cessation of trained behavior occurring within the first 30 min postirradiation, is one event which follows exposure to supralethal doses of ionizing radiation (Kimeldorf and Hunt, 1965). This dramatic alteration in motor function is characterized by a transient reduction in performance, with recovery, followed by a recurring, gradual performance decrement (PD),

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which may or may not be associated with ETI (Curran *et al.*, 1973). Irradiation-induced hypotension has been implicated as the cause of ETI found with supralethal irradiation exposure (Miletich and Strike, 1970). However, postirradiation hypotension does not occur with equal frequency in all species, having been reported in monkeys and rats but not in cats and dogs (Miletich and Strike, 1970; Chaput *et al.*, 1972; Pitchford, 1968). Likewise, ETI was not seen in dogs following irradiation exposure of up to 400 Gy (1 Gy = 100 rad) (Chaput *et al.*, 1972; Pitchford, 1968); however, a dose-related, progressive PD was reported with those animals exposed to doses of 100–300 Gy (Pitchford, 1968). A recent study reported a performance decrement in rats exposed to a 100 Gy, whole-body, bilateral dose of  $\gamma$  radiation received from a  $^{60}\text{Co}$  source (Cockerham *et al.*, 1984). ETI has been reported in monkeys (Bruner *et al.*, 1975; Franz, 1985) and in miniature swine (Chaput and Wise, 1969), although the ETI seen in swine differed from that seen in monkeys by the frequent accompaniment of convulsions and spasms of the extremities. Monkeys were selected for this study because they exhibit a transient decrement in performance similar to that described in humans who were accidentally irradiated (Hunt, 1987).

Studies have reported elevations of circulating blood histamines in humans undergoing radiation therapy (Lasser and Stenstrom, 1954), and increases in nonhuman primate plasma histamine levels (Alter *et al.*, 1983; Cockerham *et al.*, 1986a) following irradiation. Histamine may be implicated in radiation-induced hypotension (Alter *et al.*, 1983) and in postirradiation reduced cerebral blood flow (Cockerham *et al.*, 1986a). Also, antihistamines have been used to modify the irradiation-induced release of histamine and early transient incapacitation in the monkey (Doyle *et al.*, 1974; Doyle and Strike, 1977).

The release of histamine from mast cells by ionizing radiation may not be effected directly, but may employ an intermediate chemical mediator such as neurotensin. Re-

ports of *in vivo* neurotensin-mediated release of histamine include rat whole-body infusion (Oishi *et al.*, 1983), rat hindquarter perfusion (Kerouac *et al.*, 1984), and rat head perfusion (Rioux *et al.*, 1985) experiments. Pretreatment with the mast cell stabilizer, disodium cromoglycate (DSCG, cromolyn sodium), inhibited the neurotensin-induced release of histamine (Carraway *et al.*, 1982; Cochrane *et al.*, 1986; Kerouac *et al.*, 1984; Oishi *et al.*, 1983; Rioux *et al.*, 1985), and was successful in diminishing the radiation-induced decrease in cerebral blood flow (Cockerham *et al.*, 1986b).

In the present study we attempt to evaluate further the effect of DSCG on radiation-released histamine, postradiation hypotension, and reduced regional cerebral blood flow (rCBF) in two contrasting regions of the brain. Two regions of the brain not previously studied (Cockerham *et al.*, 1986a,b) were selected for the determination of blood flow in this study. The hippocampus was selected as the first region of interest because this area of the brain is particularly vulnerable to oxygen deprivation (Kirino and Sano, 1984; Suzuki *et al.*, 1983). The second region of interest, the visual cortex, is an area that may be involved with the reduced visual discrimination performance seen in the monkey following 50 Gy  $\gamma$ -neutron radiation (de Haan *et al.*, 1969) and, also, is reported to show changes in neuronal activity following ischemia (Suzuki *et al.*, 1983). We also attempt to determine if the postirradiation systemic plasma levels of histamine and neurotensin are changed with DSCG and antihistamine pretreatment.

The purpose of this investigation, therefore, is threefold: first, to determine if the combined use of DSCG and antihistamines affects the irradiation-induced release of histamine, postirradiation hypotension, and reduced regional cerebral blood flow; second, to determine if the systemic plasma level of neurotensin is changed significantly following irradiation; and finally, if there is an irradiation-induced release of neurotensin, to de-

termine if DSCG will inhibit the neurotensin-induced release of histamine in primates.

Understanding the physiological basis for irradiation-induced incapacitation and shock is essential to providing protection against these irradiation effects, for interpreting the effects of nuclear accidents, and for predicting the effects of nuclear warfare in order to prepare for casualty treatment.

### MATERIALS AND METHODS

Sixteen rhesus monkeys (*Macaca mulatta*), weighing between 2.3 and 3.5 kg ( $2.9 \pm 0.08$  SE), were used in this study. The animals were divided randomly into two groups of six animals each and one group of four animals, as follows: Group I—six sham-irradiated monkeys; Group II—six irradiated monkeys; and Group III—four monkeys given an iv infusion of physiological saline containing the  $H_1$  blocker mepyramine (pyrilamine) (0.5 mg/min) and the  $H_2$  blocker cimetidine (0.25 mg/min) for 1 hr before and for 1 hr after irradiation, and the mast cell stabilizer DSCG by iv infusion (100 mg/kg) 5 min before irradiation. Food was withheld from all animals for 18 hr before the experiment, but water was available *ad libitum*. Research was conducted according to the principles enunciated in the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources, National Research Council. The monkeys were initially anesthetized in their cages with an im injection of ketamine hydrochloride (20 mg/kg) with 0.015 mg/kg atropine sulfate and were then moved to the laboratory where the remainder of the experiment was conducted.

A systemic venous catheter was used to administer physiological saline and the primary anesthetic,  $\alpha$ -chloralose (100 mg), with supplemental infusions provided as needed, based on heart rate, blood pressure, respiration rate, blood pH, and peripheral reflexes. A femoral arterial catheter was used to withdraw blood for blood chemistry and blood gas determinations and to measure systemic arterial blood pressure via a Statham P23 Db pressure transducer.

Approximately 2 hr before irradiation or sham-irradiation, the animals were intubated with a cuffed endotracheal tube and ventilated using a forced volume respirator to maintain a stable blood pH and oxygen tension. After insertion of the endotracheal tube, each animal was placed on a circulating water blanket to maintain body temperature between 36 and 38°C. A rectal probe was inserted to monitor body temperature.

The animal's head was positioned on the headholder of a stereotaxic instrument (David Kopf Instruments, Tujunga, CA) and the scalp was shaved and incised, al-

lowing access to the skull. Using the stereotaxic micromanipulator, the skull was marked for insertion of four electrodes and small burr holes were drilled through the skull at these marks. Again, using the micromanipulator, one electrode was placed in the left and one in the right hippocampus (Snider and Lee, 1961). In the same manner, one electrode was placed in the left and one in the right visual cortex, 4 mm to each side of the longitudinal fissure. The latter two electrodes were placed so that the tips were 2.5 mm below the surface to ensure that measurements would be taken from the cortical grey matter. The electrodes were Teflon-coated, platinum-iridium wire of 0.178-mm diameter, encased in, but insulated from, rigid stainless-steel tubing (22-ga spinal needle) with exposed tips of approximately 2 mm. The exposed dura was covered with moistened pledgets and the electrodes were sealed and secured to the skull with dental acrylic. A stainless-steel reference electrode was placed in neck tissue.

Regional cerebral blood flow was measured by the hydrogen clearance technique for 30 min before irradiation or sham-irradiation and for 60 min after. This technique is essentially an amperometric method, which measures the current induced in a platinum electrode by the reduction of hydrogen. The current produced has a linear relationship with the concentration of hydrogen in the tissue (Hyman, 1961). Hydrogen was introduced into the blood via inhalation through the endotracheal tube at a rate of approximately 5% of the normal respiratory intake for each flow measurement. Blood flow was measured by each of the four electrodes every 10 min. The electrodes were maintained electrically at +600 mV in respect to the reference electrode, to reduce possible oxygen and ascorbate interference. This method has been successfully employed in several similar studies (Cockerham *et al.*, 1986a,b).

After 30 min of recording, the animals were disconnected from the respirator and recording apparatus to facilitate irradiation in a separate room. The animals were reconnected to the respirator and recording apparatus at 4 min postirradiation or sham-irradiation and measurements were continued for a minimum of 60 min. At 30 and 10 min preirradiation or sham-irradiation, and at 2, 4, 6, 15, 30, 45, and 60 min postirradiation or sham-irradiation, blood samples were taken via the arterial catheter to determine plasma histamine and neurotensin levels. Blood samples were also taken to monitor stability of blood pH and oxygen tension, and respiration was adjusted to maintain preirradiation levels. Mean systemic arterial blood pressure was determined via the arterial catheter for the duration of the experiment. After termination of the measurements, while still under anesthesia, the animals were humanely euthanized with an iv injection of saturated  $MgSO_4$ , and the electrodes were examined visually via dissection for verification of placement.

Blood samples for plasma histamine and neurotensin determinations were drawn from the arterial catheter

with plastic syringes and transferred to prelabeled, chilled collection tubes containing EDTA. The tubes were inverted gently and stored on ice until the termination of the experiment. The blood was then centrifuged (5°C) and the plasma was transferred to polypropylene tubes, rapidly frozen, and maintained at -80°C until analyzed. Plasma levels of histamine were determined by the specific, radioenzymatic assay for histamine described by Carraway *et al.* (1982). Plasma levels of neurotensin were measured using a method previously described by Carraway *et al.* (1980). The antiserum, HC-8, used in this method has been characterized earlier (Carraway and Leeman, 1976) and is directed primarily toward the C-terminal, biologically active portion of the neurotensin molecule, cross-reacting 50% with NT<sup>8-13</sup> and <0.01% with NT<sup>1-10</sup>.

Irradiation was accomplished with a bilateral, whole-body exposure to  $\gamma$ -ray photons from a cobalt-60 source located at the Armed Forces Radiobiology Research Institute. Exposure was limited to a mean of 1.38 min at 74 Gy/min steady state, free-in-air. Dose rate measurements at depth were made with an ionization chamber placed in a tissue equivalent model. The measured mid-line tissue dose rate was 69 Gy/min, producing a calculated total dose of 100 Gy, taking into account the rise and fall of the radiation source.

Blood pressure and blood flow data were grouped into 10-min intervals, measured in relation to midtime of radiation, and plotted at the middle of the interval. The Wilcoxon rank sum test was used for the statistical analysis of the data. A 95% level of confidence was employed to determine significance. Since all the animals were treated identically before irradiation or sham-irradiation, and since the preradiation data for the control and test animals showed no significant difference, the preradiation data for the irradiated and sham-irradiated animals were combined.

## RESULTS

As seen in Fig. 1, the mean systemic arterial blood pressure (MABP) of untreated, irradiated animals decreased to 23% of the preradiation mean of  $106.0 \pm 3.41$  mm Hg within 10 min postirradiation. This was followed by a steady decline to a 60-min postirradiation level that was 12% of the preradiation values. After sham-irradiation there was no significant change in MABP for the six control monkeys. The four treated, irradiated monkeys (Group III) displayed a MABP that was statistically different from the untreated, irradiated monkeys at all postirradiation

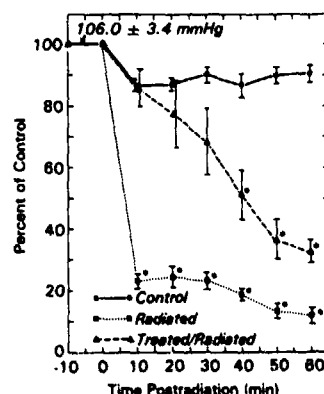


FIG. 1. Percentage change in mean arterial blood pressure after exposure to 100 Gy, whole-body,  $\gamma$  irradiation ( $\pm$  SEM) compared to a preradiation mean of  $106.0 \pm 3.41$  mm Hg. Animals in the sham-irradiated group ( $n = 6$ ) were given physiological saline for 60 min before and after sham-irradiation. The untreated, irradiated group ( $n = 6$ ) also received saline but were exposed to 100 Gy  $\gamma$  irradiation. The treated, irradiated group ( $n = 4$ ), in addition, received mepyramine (0.5 mg/min) and cimetidine (0.25 mg/min) in the saline infusion and disodium cromoglycate (DSCG) by iv infusion (100 mg/kg) 5 min before irradiation (\*, Significantly different from controls;  $p = 0.05$ ).

times of observation but displayed a significant difference from the controls only after the 30-min postirradiation time. The respiration of each subject was maintained at preradiation levels and, although not presented, the blood gas data revealed a general stability of blood pH and oxygen tension throughout the experimental period.

The preradiation cortical blood flow, as shown in Fig. 2, was  $60.8 \pm 5.5$  ml per 100 g of tissue per minute. The postirradiation blood flow for the sham-irradiated group of monkeys showed no significant changes for the 60-min observation period while the values for the untreated, irradiated monkeys showed a steady decline to 29% of the preradiation levels by 60 min postirradiation. These levels became significantly different ( $p = 0.05$ ) from those of the sham-irradiated group at 10 min postirradiation and remained that way for the remainder of the observations. In contrast, the cortical blood flow

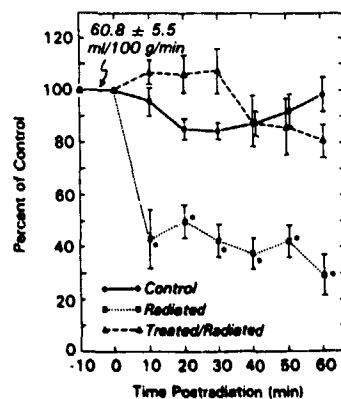


FIG. 2. Percentage change in cortical blood flow after exposure to 100 Gy, whole-body,  $\gamma$  irradiation ( $\pm$  SEM) compared to a preirradiation mean of  $60.8 \pm 5.5$  ml/g of tissue/min. Animals in the sham-irradiated group ( $n = 6$ ) were given physiological saline for 60 min before and after sham-irradiation. The untreated, irradiated group ( $n = 6$ ) also received saline but were exposed to 100 Gy  $\gamma$  irradiation. The treated, irradiated group ( $n = 4$ ), in addition, received mepyramine (0.5 mg/min) and cimetidine (0.25 mg/min) in the saline infusion and disodium cromoglycate (DSCG) by iv infusion (100 mg/kg) 5 min before irradiation (\*, Significantly different from controls;  $p = 0.05$ ).

in the treated, irradiated monkeys actually increased for the first 30 min postirradiation and never decreased to less than 80% of the preirradiation levels at any time postirradiation. For any of the postirradiation observations, there was no significant difference between the treated, irradiated group and the control group. However, a statistically significant difference ( $p = 0.05$ ) did exist between the untreated, irradiated group and the other two groups from 10 min postirradiation through the remainder of the measurements.

Figure 3 displays a preirradiation mean blood flow of  $75.1 \pm 5.9$  ml per 100 g of tissue per minute in the hippocampus. The postirradiation blood flow values for the untreated, irradiated animals showed a rapid, significant decline to 32% of the preirradiation levels within 10 min postirradiation. Following an increase to 43% below preradiation levels at 30 min postirradiation, the values then decreased to 23% of the preirradiation levels by

60 min postirradiation. There was a significant difference ( $p = 0.05$ ) between the untreated, irradiated group of monkeys and the other two groups at all postirradiation times of measurement. At all postirradiation periods of observation the hippocampal blood flow of the treated, irradiated animals was not significantly different from that of the sham-irradiated monkeys.

Figure 4 displays a preirradiation mean plasma neurotensin level of  $20.2 \pm 2.3$  fmol/ml. The postirradiation levels in the untreated, irradiated and the sham-irradiated animals did not differ significantly from this value for 60 min, even though the values for the untreated, irradiated group showed a peak at 6 min, and a gradual rise between 15 and 60 min. Although there was not a significant difference between the neurotensin levels in the treated, irradiated monkeys and that found in the other two groups, the maximum level in the treated group did occur 10

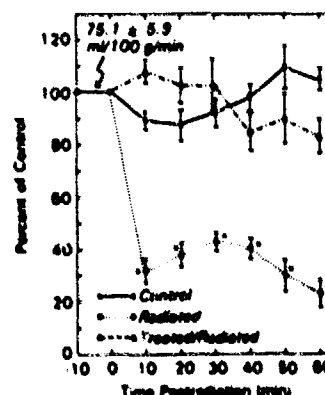


FIG. 3. Percentage change in hippocampal blood flow after exposure to 100 Gy, whole-body,  $\gamma$  irradiation ( $\pm$  SEM) compared to a preirradiation mean of  $75.1 \pm 5.9$  ml/g of tissue/min. Animals in the sham-irradiated group ( $n = 6$ ) were given physiological saline for 60 min before and after sham-irradiation. The untreated, irradiated group ( $n = 6$ ) also received saline but were exposed to 100 Gy  $\gamma$  irradiation. The treated, irradiated group ( $n = 4$ ), in addition, received mepyramine (0.5 mg/min) and cimetidine (0.25 mg/min) in the saline infusion and disodium cromoglycate (DSCG) by iv infusion (100 mg/kg) 5 min before irradiation (\*, Significantly different from controls;  $p = 0.05$ ).

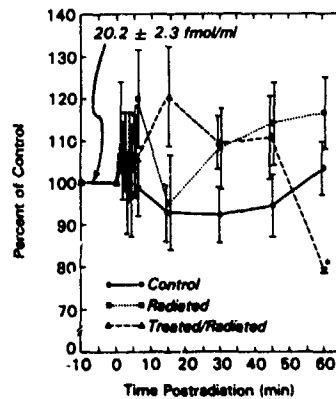


FIG. 4. Percentage change in plasma neurotensin concentration after exposure to 100 Gy, whole-body,  $\gamma$  irradiation ( $\pm$  SEM) compared to a preirradiation mean of  $20.2 \pm 2.3$  fmol/ml. Animals in the sham-irradiated group ( $n = 6$ ) were given physiological saline for 60 min before and after sham-irradiation. The untreated, irradiated group ( $n = 6$ ) also received saline but were exposed to 100 Gy  $\gamma$  irradiation. The treated, irradiated group ( $n = 4$ ), in addition, received mepyramine (0.5 mg/min) and cimetidine (0.25 mg/min) in the saline infusion and disodium cromoglycate (DSCG) by iv infusion (100 mg/kg) 5 min before irradiation (\*, Significantly different from controls;  $p = 0.05$ ).

min later postirradiation than in the untreated animals.

The preirradiation plasma histamine level, as shown in Fig. 5, was  $0.58 \pm 0.06$  ng/100  $\mu$ l. The postirradiation levels for the sham-irradiated group of monkeys showed no significant changes for 60 min of observation. During this same period the levels for both irradiated groups showed abrupt, significant increases at the 2-min point to levels that were almost 1600% above the preirradiation level. Significant differences were also present between both of the irradiated monkey groups and the sham-irradiated animals at the 4- and 6-min points. The histamine levels of the treated, irradiated group were also significantly higher than those found in the sham-irradiated monkeys at the 15-min time. At no time postirradiation were the plasma histamine levels of the treated, irradiated and the nontreated, irradiated monkeys significantly different. The histamine levels of the

irradiated monkeys were significantly lower than for the sham-irradiated monkeys at the 60-min postirradiation point.

## DISCUSSION

The initial precipitous decline in postradiation rCBF reported here has been well documented in the rhesus monkey (Chapman and Young, 1968; Cockerham *et al.*, 1986a; Cockerham *et al.*, 1986b). This decline has been associated with the immediate decrease in MABP and a critical MABP of 50 to 60% of normal is said to be necessary for adequate autoregulation of cerebral circulation (Chapman and Young, 1968; Doyle *et al.*, 1974; Farrar *et al.*, 1981). A similar, drug-induced decrease in cerebral blood flow accompanied by symptoms and signs of cerebral ischemia has been reported in man (Finnerty *et al.*, 1957), and on the basis of the diminished ce-

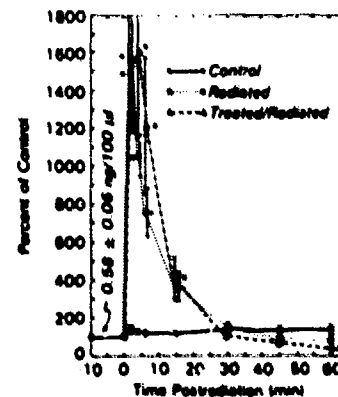


FIG. 5. Percentage change in plasma histamine concentration after exposure to 100 Gy, whole-body,  $\gamma$  irradiation ( $\pm$  SEM) compared to a preirradiation mean of  $0.58 \pm 0.06$  ng/100  $\mu$ l. Animals in the sham-irradiated group ( $n = 6$ ) were given physiological saline for 60 min before and after sham-irradiation. The untreated, irradiated group ( $n = 6$ ) also received saline but were exposed to 100 Gy  $\gamma$  irradiation. The treated, irradiated group ( $n = 4$ ), in addition, received mepyramine (0.5 mg/min) and cimetidine (0.25 mg/min) in the saline infusion and disodium cromoglycate (DSCG) by iv infusion (100 mg/kg) 5 min before irradiation (\*, Significantly different from controls;  $p = 0.05$ ).

rebral blood flow reported in these animals one might expect a severe functional impairment of the CNS in monkeys following irradiation. In fact, the decline in MABP and rCBF reported here corresponds closely in time with the observed occurrence of irradiation-induced ETI (Curran *et al.*, 1973; Doyle *et al.*, 1974; Bruner, 1977) and suggests a temporal relationship between the depressed MABP, the decreased rCBF, and the appearance of ETI. However, the infusion of monkeys with either saline or norepinephrine after irradiation in an attempt to block hypotension produced no significant difference between the performance of monkeys in which the blood pressure was maintained with norepinephrine and the performance of monkeys that were injected with saline (Turns *et al.*, 1971). Therefore, if there is a causal relationship, as well as a temporal, it seems to exist between the decreased rCBF and the appearance of ETI.

The measurements of blood flow in the hippocampus of 100-Gy,  $\gamma$ -irradiated monkeys, when plotted at postradiation times (Fig. 3), present a graph strikingly similar to the performance graph of monkeys exposed to 89 Gy of mixed  $\gamma$ -neutron radiation (Curran *et al.*, 1973), with the same temporal relationship. Likewise, the abrupt increase in plasma histamine levels 2 min postradiation (Fig. 5) coincides with the initial depression in MABP (Fig. 1) and rCBF (Figs. 2 and 3), and the onset of ETI (Curran *et al.*, 1973). The role of histamine is further supported by investigators who have reported the alteration of ETI by the administration of antihistamines (Doyle *et al.*, 1974).

The plasma histamine levels found in this experiment serve to corroborate the results reported on subhuman primates by other investigators (Doyle and Strike, 1977; Alter *et al.*, 1983; Cockerham *et al.*, 1986a) by showing an immediate rise by 2 min postirradiation followed by a much slower fall to preirradiation levels by 30 min postirradiation. However, the combined administration of DSCG and  $H_1$  and  $H_2$  blocking antihista-

mines did not alter the irradiation-induced release of histamine, showing plasma histamine levels which appeared to be much like those seen in a previous report (Cockerham *et al.*, 1986a).

The postirradiation hypotension was altered significantly with the combined administration of DSCG and the antihistamines mepyramine and cimetidine. This is in contrast to a previous report using DSCG alone (Cockerham *et al.*, 1986b) in which there was not a significant difference between the DSCG-treated and the untreated postirradiation MABP. Comparison of the results of the two studies, then, suggests the involvement of the irradiation-induced release of histamine with the postirradiation hypotension, since the addition of the  $H_1$  and  $H_2$  receptor blockers resulted in an alteration of the postirradiation MABP not achieved with the administration of DSCG alone. However, the administration of DSCG alone (Cockerham *et al.*, 1986b) or in combination with antihistamines resulted in a postirradiation rCBF that was close to the same level as that found in the control animals. This, then, indicates that the irradiation-induced release of histamine was not directly responsible for the postirradiation decrease in rCBF but may be indirectly responsible through its effect on the MABP. Moreover, since the administration of DSCG did not inhibit the release of histamine or the eventual decrease in MABP, DSCG must act through a different path to prevent the irradiation-induced decrease in rCBF.

Certainly, the action of DSCG does not seem to be by blocking the neurotensin mediated release of histamine since the plasma neurotensin levels in the irradiated monkeys, while exhibiting some indications of a postirradiation increase, were not found to be significantly different from those in the sham-irradiated monkeys. However, these values do not indicate the levels in the tissues, where neurotensin may be degraded very rapidly (Emson *et al.*, 1982; Checlar *et al.*, 1982) as evidenced by a rapid disappearance of neuro-



tensin-like immunoreactivity (Dupont and Merand, 1978).

Even though a temporal relationship does seem to exist between the release of histamine, a reduced MABP, decreased rCBF, and early transient incapacitation, the presence of other factors must be considered. Neurotensin could still conceivably be released by irradiation, cause the release of histamine from mast cells (Carraway *et al.*, 1982; Cochrane *et al.*, 1982; Cochrane *et al.*, 1986; Kerouac *et al.*, 1984; Rioux *et al.*, 1985), and trigger cerebrovascular vasoconstriction and cerebral edema (Rioux *et al.*, 1985).

The irradiation-induced reduction in rCBF may also employ intermediate mediators such as free radicals (Ohmori *et al.*, 1979) produced with exposure to ionizing radiation (Del Maestro, 1980; Kennedy *et al.*, 1984). Free radical interactions have been implicated in a large number of pathological conditions including radiation injury, ischemia, microvascular injury, and cell damage (Del Maestro *et al.*, 1980; Del Maestro, 1980; Hammond *et al.*, 1985; Kontos, 1985). The triphasic cerebral ischemic response seen after irradiation (Cockerham *et al.*, 1986a,b) may be even more damaging than complete ischemia (Rehncrona *et al.*, 1980) since reperfusion may lead to the formation of additional free radicals (Julicher *et al.*, 1984; Peterson *et al.*, 1985). A possible mode of pharmacologic intervention may well be the introduction of DSCG to intervene in the production of free radicals (Carmichael *et al.*, 1987), thereby explaining why treatment with DSCG would maintain rCBF during the entire observation period even with the presence of profound hypotension in treated animals at 60 min. Thus, the DSCG prevention of irradiation-induced free radical formation would allow the maintenance of rCBF in the initial 20–30 min. Therefore, there would be no reperfusion-induced formation of additional free radicals, allowing the rCBF to be maintained during the second portion of the observation period.

In conclusion, we have shown that the combined administration of DSCG and the antihistamines mepyramine and cimetidine did not alter significantly the irradiation-induced release of histamine or the postirradiation plasma levels of neurotensin. We were not able to demonstrate whether DSCG would inhibit the postirradiation, neurotensin-induced release of histamine. However, we were able to demonstrate that DSCG and the antihistamines mepyramine and cimetidine, given in combination, will alter significantly the postirradiation hypotension and the reduced regional cerebral blood flow. We have also introduced a theoretical mechanism through which the administration of DSCG may prevent an irradiation-induced reduction in rCBF. The next logical steps will be to (1) show that DSCG actually does prevent the irradiation-induced production of free radicals, and (2) determine if the administration of DSCG diminishes irradiation-induced ETI.

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